Adulthood residential ultraviolet radiation, sun sensitivity, dietary vitamin D, and risk of lymphoid malignancies in the California Teachers Study

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To lend clarity to inconsistent prior findings of an inverse association between ultraviolet radiation (UVR) exposure and risk of lymphoid malignancies, we examined the association of prospectively ascertained residential ambient UVR exposure with risk of non-Hodgkin lymphomas (NHLs), multiple myeloma (MM), and classical Hodgkin lymphoma in the California Teachers Study cohort. Among 121 216 eligible women, 629 were diagnosed with NHL, 119 with MM, and 38 with Hodgkin lymphoma between 1995-1996 and 2007. Cox proportional hazards regression was used to estimate incidence rate ratios (RRs) with 95% confidence intervals (CIs). Residential UVR levels within a 20-km radius were associated with reduced risk of overall NHL (RR for highest vs lowest statewide quartile of minimum UVR [≥ 5100 vs < 4915 W-h/m^2], 0.58; 95% CI, 0.42-0.80), especially diffuse large B-cell lymphoma (RR, 0.36; 95% CI, 0.17-0.78) and chronic lymphocytic leukemia/small lymphocytic lymphoma (RR, 0.46; 95% CI, 0.21-1.01), and MM (RR for maximum UVR, 0.57; 95% CI, 0.36-0.90). These associations were not modified by skin sensitivity to sunlight, race/ethnicity, body mass index, or neighborhood socioeconomic status. Dietary vitamin D also was not associated with risk of lymphoid malignancies. These results support a protective effect of routine residential UVR exposure against lymphomagenesis through mechanisms possibly independent of vitamin D. (*Blood*. 2011;118(6):1591-1599)

Introduction

During the past decade, several case-control studies have shown an inverse association between intensity of childhood or adulthood exposure to ultraviolet radiation (UVR) and risk of non-Hodgkin lymphomas (NHL; reviewed in Negri[1]). These findings were supported by a pooled analysis of 10 NHL case-control studies, in which recreational UVR exposure was associated with a reduced risk of overall and subtype-specific NHL.[2] The effect of UVR exposure on risk of multiple myeloma (MM) and Hodgkin lymphoma (HL) is less well studied. The suggested hypothesis for the protective effect of UVR on NHL development involves UVR-mediated activation of vitamin D, which has antiproliferative and pro-differentiative effects on lymphocytes.[3]

One limitation of most existing studies of the relation between UVR exposure and risk of lymphoid malignancies is their retrospective nature. Compared with well-designed prospective cohort studies, retrospective studies, including those of sun exposure,[4] are probably more affected by recall, selection, and survival biases. To our knowledge, only 2 prospective studies, both based in Scandinavia, have examined the relation between UVR and risk of NHL. With the use of UVR exposure estimated by inference from job titles and latitude of work and home addresses[5] or by self-report of sunburn, sunbathing, and sunlamp use history,[6] neither study found an association with NHL risk, offering a striking contrast to the results of most retrospective studies. Given the inconsistency of results even before the more recent prospective study,[6] an expert panel has determined that the epidemiologic evidence about the association between UVR exposure and NHL risk is insufficient to reach any clear conclusions.[7]

Understanding the role of UVR in the cause of lymphoid malignancies is of public health importance because few modifiable risk factors have been identified for NHL, MM, or HL, which together account for > 109 000 new cancer cases and 36 000 deaths per year in the United States.[8] If modestly increasing UVR exposure or augmenting dietary vitamin D intake can help prevent lymphomagenesis, then these actions might serve as readily modifiable protective measures. Therefore, we investigated whether estimated residential UVR exposure, dietary vitamin D intake, and skin sensitivity to sunlight, which affects both sun-related behaviors and UVR-mediated vitamin D synthesis,[9] are associated with risk of lymphoid malignancies among women in the large, prospective California Teachers Study (CTS) cohort.

Methods

Study population

The CTS cohort comprises 133 479 active and retired female public school teachers and administrators who, in 1995-1996, completed a mailed, self-administered baseline questionnaire that evaluated a range of risk factors for cancer and women's health. For this analysis, we sequentially

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excluded participants who, at baseline, were not residents of California (n = 8867); had an unknown prior history of cancer (n = 663); consented to participate only in analyses of breast cancer (n = 18); had previously been diagnosed with NHL, MM, HL, or leukemia (n = 536); or were ≥ 85 years of age (n = 2179). Of the 121 216 remaining women included in this analysis, 629 were diagnosed with NHL (including chronic lymphocytic leukemia/small lymphocytic lymphoma [CLL/SLL]; International Classification of Diseases–Oncology, 3rd edition [ICD-O-3] morphology codes 9590-9591, 9670-9729, 9761, 9764, 9820, 9823, 9827, 9831-9837, 9940, 9948, and 9970), 119 were diagnosed with MM (including plasmacytoma; ICD-O-3 codes 9731-9734), and 38 were diagnosed with classical HL (ICD-O-3 codes 9650-9655 and 9661-9667)][10] after joining the cohort and through December 31, 2007. The 3 most commonly diagnosed NHL histologic subtypes in the cohort were diffuse large B-cell lymphoma (DLBCL; n = 155; ICD-O-3 codes 9678-9680 and 9684), follicular lymphoma (FL; n = 122; ICD-O-3 codes 9690, 9691, 9695, and 9698), and CLL/SLL (n = 125; ICD-O-3 codes 9670 and 9823).

Human subject research in this study was approved by the institutional review boards at all participating institutions. Informed consent was obtained in accordance with the Declaration of Helsinki.

Skin sensitivity

To measure skin sensitivity to sunlight exposure, participants were asked at baseline to report what would happen to their skin if they were in the hot sun for 1 hour without protection (severe burn with blistering, severe burn without blistering, mild burn then tan or darken, no burn but tan or darken, or no burn or tan); what would eventually happen to their skin if they were in the sun repeatedly (deeply tan or darken, moderately tan or darken, lightly tan or darken, or would not tan or darken); whether they had ever been sunburned severely enough to cause blistering (yes or no); and, if yes to the last question, at what age it first occurred (≤ 5, 6-10, 11-15, 16-20, 21-25, or ≥ 26 years) and how often it had occurred (1-2, 3-4, 5-9, or ≥ 10 times). Participants also reported their personal history of melanoma or other skin cancer.

Residential UVR and socioeconomic status

We geocoded participants' residential addresses at baseline (available for 95% of California residents; those with post office boxes or missing addresses were not geocoded) and any subsequent addresses reported during follow-up. Complete address information at baseline and follow-up was available for 91% of participants (including 61% who did not move from their baseline address), baseline address only was available for 2%, baseline and partial follow-up addresses were available for 2%, follow-up address(es) only were available for 2%, and no geocodable addresses were available for 3%. We linked the latitude and longitude data to a UVR exposure database that uses hourly measures of ambient UVR exposure gathered from 237 US radiation stations (including 5 in California) that contribute measurements to the National Solar Radiation Database.[11,12] With the use of these measurements, we developed a geographic information systems model, accounting for local climate and terrain features that affect UVR at the earth's surface, to estimate average daily total global solar radiation (henceforth referred to as "UVR") at the 1-km^2 ground surface level for the entire continental United States from 1961 through 2007. The validity of this approach for estimating UVR at unsampled locations throughout the continental United States, including California[12] and in epidemiologic studies,[11] has previously been published. Because UVR was equally well estimated by the modeling approach in each decade, and we observed no appreciable differences in year-specific UVR over time,[12] we used a single summary UVR measure that incorporated all data from the National Solar Radiation Database for each geographic location.[11,12]

To allow for variation in individual UVR exposure because of local travel, we created 20-km buffers of exposure around each residential point location, then derived the median, minimum, and maximum UVR (in watt-hours per m^2 [W-h/m^2]) within each buffer zone. We summed exposures over an arbitrary 20-km buffer to account for the fact that local travel might cover areas of various ground-level UVR and that home residence exposures may not accurately reflect a person's usual maximum or minimum exposure. For example, someone who lived inland but worked or frequently spent weekends near the coast would probably have a wider range of UVR exposures than someone who lived and worked inland. For participants who changed residential addresses after baseline, we updated UVR exposure to match each new address, beginning at the date of relocation, thereby making the exposure time dependent. During time periods when a participant was known to have moved but the address was a post office box or missing, UVR exposure was classified into a separate "missing" category.

Because the baseline CTS questionnaire did not assess participants' socioeconomic status (SES), we obtained a neighborhood-level measure of each participant's SES by geocoding participants' residential addresses at baseline to census block groups and using data from the 1990 US Census to rank all block groups in California according to statewide deciles of a composite SES index, including education, income, and occupation.[13]

Dietary assessment

Dietary intake during the year before baseline (1995, for most women) was assessed with the use of an early version of the 1995 Health History and Habits food frequency questionnaire (FFQ) developed by Dr Gladys Block.[14] Women were asked how often, on average, they consumed 103 food and beverage items or groups per month, week, or day, and whether they usually consumed a small, medium, or large serving size of each item, relative to a standard "medium" serving size. Women who reported taking vitamins or minerals once or more per week were asked how many days per week, for how many years, and at what dosage they had taken multivitamins, vitamin A, β-carotene, vitamin C, vitamin E, and selenium. The Block nutrient database was updated to include current nutrient compositions and vitamin D from foods and beverages.[15,16]

In this analysis, we focused on total (from food and multivitamins) and dietary (from food only) vitamin D, as well as total and dietary calcium and dietary retinol, because the latter 2 micronutrients are negative regulators of biologically available vitamin D.[17] In a validation/calibration study of the FFQ in a subset of cohort members, estimates of reliability, as measured by correlations between 2 FFQs spaced 10 months apart, were 0.77 for vitamin D and 0.74 for calcium. Estimates of validity, relative to four 24-hour dietary recalls, were 0.64-0.78 for vitamin D and 0.67-0.77 for calcium (measures not calculated for retinol).[18] We also assessed total consumption of fish or seafood as major dietary sources of vitamin D, and total consumption of dairy products as major dietary sources of calcium.

Follow-up

Participants were followed from the date of completion of the baseline questionnaire until the earliest of the following events: date of first diagnosis with a hematopoietic malignancy, relocation out of California, death, or December 31, 2007. Participants diagnosed with leukemia (n = 136) were censored at the date of diagnosis; in analyses of specific lymphoid malignancies, participants diagnosed with any other hematopoietic cancer were also censored. Incident cancers were ascertained through annual linkage of the CTS cohort to the population-based California Cancer Registry, which is > 99% complete and has high standards of data quality control, including reliable distinction of lymphoma histologic subtypes.[19] Linkages with the California state mortality file, the national Social Security Administration death master file, and the National Death Index were used to ascertain date and cause of death. Address changes were obtained through record linkages with multiple sources, including the National Change of Address database, change-of-address forms from annual mailed newsletters, and proactive notifications by participants.

Statistical analysis

Associations between skin sensitivity to sunlight, residential UVR, or micronutrient or food intake and risk of lymphoid malignancies were estimated with Cox proportional hazards regression, with age (in days) as

Table 1. Baseline (1995-1996) demographic characteristics of California Teachers Study cohort members eligible for analysis (N = 121 216)

Characteristic	n (%)
Age, y	
20-29	5373 (4)
30-39	15 827 (13)
40-49	32 280 (27)
50-59	30 122 (25)
60-69	20 555 (17)
70-79	13 556 (11)
80-84	3503 (3)
Race/ethnicity	
White, non-Hispanic	104 815 (86)
Other race/ethnicity	15 405 (13)
Missing	996 (1)
Body mass index	
< 25 kg/m^2	70 857 (58)
25 to < 30 kg/m^2	29 104 (24)
≥ 30 kg/m^2	16 479 (14)
Missing	4776 (4)
Neighborhood socioeconomic status (statewide quintiles)	
1st (lowest)	4437 (4)
2nd	14 255 (12)
3rd	20 507 (17)
4th	36 153 (30)
5th (highest)	44 318 (37)
Missing	1546 (1)
Skin reaction to hot sun exposure without protection for 1 h	
Severe burn with blistering	16 131 (13)
Severe burn without blistering	25 260 (21)
Mild burn, then tan or darken	55 139 (45)
No burn	22 342 (18)
Missing	2344 (2)
Skin reaction to repeated sun exposure	
Deep tan or darkening	27 495 (23)
Moderate tan or darkening	52 893 (44)
Light or no tan or darkening	37 268 (31)
Missing	3560 (3)
History of blistering sunburn	
No	39 342 (32)
Yes, first at age ≤ 10 y	19 150 (16)
Yes, first at ages 11-15 y	27 615 (23)
Yes, first at ages 16-20 y	21 274 (18)
Yes, first at age ≥ 21 y	11 059 (9)
Yes, missing age	831 (1)
Yes, 1-2 times	33 628 (28)
Yes, 3-4 times	22 312 (18)
Yes, ≥ 5 times	21 675 (18)
Yes, missing number of times	2314 (2)
Missing	1945 (2)
History of melanoma or other skin cancer	
No	108 432 (89)
Yes	12 784 (11)
Minimum baseline residential ultraviolet radiation in 20-km radius (W-h/m^2, based on statewide quartiles)	
< 4915	47 797 (39)
4915 to < 5026	41 682 (34)
5026 to < 5100	11 680 (10)
≥ 5100	13 920 (11)
Missing	6137 (5)
Median baseline residential ultraviolet radiation in 20-km radius (W-h/m^2, based on statewide quartiles)	
< 4915	32 324 (27)
4915 to < 5026	26 615 (22)
5026 to < 5100	29 453 (24)
≥ 5100	26 687 (22)
Missing	6137 (5)
Maximum baseline residential ultraviolet radiation in 20-km radius (W-h/m^2, based on statewide quartiles)	
< 4915	29 051 (24)
4915 to < 5026	15 245 (13)
5026 to < 5100	22 869 (19)
≥ 5100	47 914 (40)
Missing	6137 (5)

the timescale and stratified by age (in years) at baseline to adjust for calendar-year effects. Incidence rate ratios (RRs) were estimated as hazard ratios with 95% confidence intervals (CIs). Median, minimum, and maximum residential UVRs were categorized into quartiles on the basis of the California statewide distribution of UVR, to make results more generalizable and to encompass a more balanced distribution of UVR exposure. Total and dietary intakes of micronutrients and consumption of seafood and dairy products were categorized into quartiles on the basis of the distribution in the cohort. For both sets of variables, the lowest quartile served as the reference group. Likelihood ratio tests for trend were conducted with each exposure coded as an ordinal variable with the use of the median of each quartile. Tests for nonlinearity of trend were based on likelihood ratio tests that compared models with each exposure coded as an ordinal versus categorical variable.[20]

We assessed the potential confounding effects of a range of factors, including race/ethnicity, birthplace, body mass index, total energy intake, vitamin use, alcohol consumption, family history of hematopoietic cancer, number of older siblings, age at menarche, oral contraceptive use, menopausal status and hormone therapy use, pesticide/herbicide/insecticide use at various ages, urban/rural residence, school employment, and neighborhood SES, but we found that none of these factors altered the associations of interest by as much as 10% after multivariable adjustment. Consequently, the final regression models were adjusted only for age and calendar-year effects. Models for intake of total vitamin D, total calcium, and dietary retinol were mutually adjusted, and models for intake of dietary vitamin D, dietary calcium, and dietary retinol were mutually adjusted.

To assess heterogeneity of the association between residential UVR and risk of overall NHL, we performed analyses stratified by factors that may modulate UVR-related behaviors or vitamin D synthesis, including all measures of skin sensitivity to sunlight, self-reported personal history of melanoma or other skin cancer, race/ethnicity, body mass index, and neighborhood SES, as well as season of diagnosis among cases. We also tested for statistical effect modification by including cross-product terms in the regression models. To test for heterogeneity of risk associations with residential UVR or skin sensitivity across lymphoma subtypes (excluding HL, for which exposure categories were combined because of small numbers), we performed likelihood ratio tests comparing the combined -2 log likelihood from models for each individual subtype as the outcome with the -2 log likelihood from a model that included all subtypes as the outcome.[21]

We evaluated the proportional hazards assumption with the use of significance tests of interactions between the exposures (other than time-dependent UVR exposure) and the timescale, as well as visual assessment of time-to-event curves, and observed no meaningful violations. All tests of statistical significance were 2-sided. Analyses were performed with SAS Version 9.2 (SAS Institute).

Table 2. RRs with 95% CIs for associations of sun sensitivity or sun exposure with risk of overall NHL, diffuse large B-cell lymphoma, and follicular lymphoma

	Overall non-Hodgkin lymphoma		Diffuse large B-cell lymphoma		Follicular lymphoma	
Sun sensitivity or exposure	**Cases (n)**	**RR (95% CI)***	**Cases (n)**	**RR (95% CI)***	**Cases (n)**	**RR (95% CI)***
Skin reaction to hot sun exposure for 1 hour without protection						
Severe burn with blistering	93	1.00 (reference)	27	1.00 (reference)	23	1.00 (reference)
Severe burn without blistering	124	0.97 (0.74-1.27)	36	0.97 (0.59-1.60)	21	0.64 (0.35-1.16)
Mild burn, then tan or darken	271	0.95 (0.75-1.20)	60	0.72 (0.46-1.13)	56	0.77 (0.48-1.26)
No burn	128	0.95 (0.72-1.24)	30	0.74 (0.44-1.25)	19	0.59 (0.32-1.08)
Skin reaction to repeated sun exposure						
Deep tan or darkening	136	1.00 (reference)	33	1.00 (reference)	27	1.00 (reference)
Moderate tan or darkening	280	0.99 (0.81-1.22)	69	1.01 (0.66-1.52)	53	0.97 (0.61-1.54)
Light or no tan or darkening	191	0.90 (0.72-1.12)	51	0.99 (0.64-1.54)	37	0.91 (0.56-1.50)
Age at first blistering sunburn, y						
Never	193	1.00 (reference)	56	1.00 (reference)	29	1.00 (reference)
≤ 10	82	0.96 (0.74-1.24)	22	0.91 (0.55-1.49)	18	1.36 (0.75-2.45)
11-15	154	1.21 (0.98-1.49)	37	1.01 (0.67-1.54)	31	1.56 (0.94-2.60)
16-20	119	1.15 (0.91-1.44)	24	0.80 (0.49-1.29)	23	1.46 (0.85-2.53)
≥ 21	63	1.03 (0.77-1.37)	14	0.79 (0.44-1.42)	16	1.78 (0.97-3.28)
Number of times with blistering sunburn						
Never	193	1.00 (reference)	56	1.00 (reference)	29	1.00 (reference)
1-2	182	1.08 (0.88-1.32)	44	0.90 (0.61-1.34)	36	1.43 (0.88-2.34)
3-4	127	1.20 (0.96-1.51)	26	0.86 (0.54-1.36)	31	1.91 (1.15-3.18)
≥ 5	100	1.03 (0.81-1.32)	23	0.83 (0.51-1.35)	21	1.38 (0.78-2.43)
History of melanoma or other skin cancer						
No	528	1.00 (reference)	138	1.00 (reference)	99	1.00 (reference)
Yes	101	1.11 (0.89-1.37)	17	0.70 (0.42-1.16)	23	1.49 (0.94-2.37)

*All models adjusted for age (as timescale) and calendar-year effects.

Results

As shown in Table 1, most CTS cohort members included in the analysis were non-Hispanic white women of relatively high SES, with moderate skin reactions to sunlight and a limited history of severe sunburns. Participants were fairly evenly distributed with respect to median residential UVR at baseline, reflecting the statewide membership of the cohort.

The associations between risk of lymphoid malignancies and measures of skin sensitivity to sunlight and history of intense sun exposure or any skin cancer are shown in Tables 2 and 3. The associations with risk of overall NHL, DLBCL, FL, CLL/SLL, MM, and HL were consistently null. A positive history of blistering sunburns, especially after age 21 years and 3-4 times, was at least marginally positively associated with risk of FL but not other lymphoid malignancies. These associations did not vary statistically significantly by lymphoma subtype.

Within a residential 20-km radius, both median and minimum UVR levels were statistically significantly inversely associated with risk of overall NHL, with linear dose-response trends and a somewhat stronger inverse association with minimum than median UVR (Tables 4 and 5). The inverse association with minimum residential UVR was particularly striking for risk of DLBCL and CLL/SLL, although the latter association was statistically nonsignificant, and tests for a linear dose-response trend were borderline statistically significant. In addition, maximum residential UVR was statistically significantly inversely associated with risk of MM, whereas point estimates for the association with median and minimum residential UVR were < 1.0 but statistically nonsignificant. Risk of FL or HL was not associated with any measure of residential UVR, although the associations did not vary statistically significantly by lymphoma subtype. When we repeated the analysis with the use of median, minimum, and maximum UVR at each participant's baseline residential address (instead of time-dependent UVR), the results were essentially unchanged (data not shown).

Because the strongest and most consistent associations were found with time-dependent minimum residential UVR, we examined whether associations between this exposure and overall NHL risk were modified by UVR- and vitamin-D–related characteristics (Table 6). No interactions were statistically significant, and associations did not vary by season of case diagnosis (data not shown). Minimum residential UVR was significantly inversely associated with risk of overall NHL only among participants with mild skin reactions to intense sun exposure, moderate or deep tanning after repeated sun exposure, a positive history of blistering sunburn, no history of melanoma or other skin cancer, non-Hispanic white race/ethnicity, or relatively high neighborhood SES. However, these groups were also the larger of the 2 strata of each modifier evaluated, making sample size a probable major determinant of the null results in the other groups. Although body mass index is inversely associated with serum vitamin D levels,[22] inverse associations with minimum residential UVR were detected among both normal weight (< 25 kg/m^2) and overweight (≥ 25 kg/m^2) participants.

Total and dietary intakes of vitamin D, retinol, and calcium were not associated with risk of overall NHL, DLBCL, FL, CLL/SLL, MM, or HL. For example, the RRs for overall NHL were 1.31 (95% CI, 0.89-1.93) for the highest quartile (≥ 229 IU/d) versus lowest quartile (< 94 IU/d) of dietary vitamin D intake (P_{trend} = 0.17); 1.04 (95% CI, 0.73-1.46) for the highest quartile (≥ 613 μg/d) versus lowest quartile (< 269 μg/d) of dietary retinol intake (P_{trend} = 0.92); and 0.95 (95% CI, 0.63-1.41) for the highest quartile (≥ 957 mg/d) versus lowest quartile (< 455 mg/d) of dietary calcium intake (P_{trend} = 0.83; other data not shown). When the analysis was restricted to participants who did not use

Table 3. RRs with 95% CIs for associations of sun sensitivity or exposure with risk of CLL/SLL, MM, and HL

	Chronic lymphocytic leukemia/small lymphocytic lymphoma		Multiple myeloma			Hodgkin lymphoma	
Sun sensitivity or exposure	Cases (n)	RR (95% CI)*	Cases (n)	RR (95% CI)*	$P_{heterogeneity}$ by lymphoma subtype†	Cases (n)	RR (95% CI)*
Skin reaction to hot sun exposure for 1 hour without protection							
Severe burn with blistering	15	1.00 (reference)	17	1.00 (reference)		13	1.00 (reference)
Severe burn without blistering	24	1.21 (0.63-2.30)	17	0.75 (0.38-1.46)			
Mild burn, then tan or darken	56	1.25 (0.71-2.22)	51	0.99 (0.57-1.71)		22	0.86 (0.43-1.70)
No burn	25	1.13 (0.59-2.14)	28	1.08 (0.59-1.98)	.55		
Skin reaction to repeated sun exposure							
Deep tan or darkening	30	1.00 (reference)	29	1.00 (reference)		24	1.00 (reference)
Moderate tan or darkening	50	0.78 (0.50-1.23)	41	0.67 (0.42-1.08)			
Light or no tan or darkening	36	0.73 (0.45-1.18)	42	0.90 (0.56-1.45)	.78	11	0.99 (0.48-2.02)
Age at first blistering sunburn, y							
Never	38	1.00 (reference)	45	1.00 (reference)		12	1.00 (reference)
≤ 10	18	1.11 (0.63-1.96)	13	0.67 (0.36-1.24)		13	0.93 (0.42-2.04)
11-15	25	1.02 (0.61-1.69)	21	0.73 (0.43-1.23)			
16-20	21	1.04 (0.61-1.77)	18	0.77 (0.44-1.33)		11	1.16 (0.51-2.63)
≥ 21	17	1.36 (0.77-2.42)	16	1.11 (0.63-1.97)	.67		
Number of times with blistering sunburn							
Never	38	1.00 (reference)	45	1.00 (reference)		12	1.00 (reference)
1-2	33	0.99 (0.62-1.58)	34	0.87 (0.56-1.36)		13	1.25 (0.57-2.74)
3-4	27	1.32 (0.81-2.17)	14	0.59 (0.32-1.07)		11	0.87 (0.38-1.97)
≥ 5	19	1.05 (0.60-1.83)	18	0.85 (0.49-1.47)	.25		
History of melanoma or other skin cancer							
No	102	1.00 (reference)	105	1.00 (reference)		35	1.00 (reference)
Yes	23	1.18 (0.75-1.85)	14	0.70 (0.40-1.22)	.07	3	0.68 (0.21-2.27)

*All models adjusted for age (as timescale) and calendar-year effects.
†Lymphoma subtypes include diffuse large B-cell lymphoma, follicular lymphoma, CLL/SLL, and MM.

multivitamins, vitamin A supplements, or calcium supplements (n = 44 871), dietary vitamin D, retinol, and calcium intakes remained unassociated with risk of overall NHL (n = 201 cases; data not shown). Consumption of seafood or dairy products was also unassociated with risk of NHL, DLBCL, FL, CLL/SLL, or HL (data not shown). The only exception to these null results was an inverse association between total dairy consumption and risk of MM, with an RR of 0.55 (95% CI, 0.31-0.97) for the highest quartile (≥ 402 g/d) versus lowest quartile (< 116 g/d) of dairy intake ($P_{trend} = 0.04$, $P_{nonlinearity} = 0.89$).

Table 4. RRs with 95% CIs for associations of time-dependent average annual residential UVR in a 20-km radius, categorized into California statewide quartiles, with risk of overall NHL, diffuse large B-cell lymphoma, and follicular lymphoma

	Overall non-Hodgkin lymphoma		Diffuse large B-cell lymphoma		Follicular lymphoma	
Average annual residential UVR in a 20-km radius (W-h/m^2)	Cases (n)*	RR (95% CI)†	Cases (n)*	RR (95% CI)†	Cases (n)*	RR (95% CI)†
Minimum UVR						
< 4915	284	1.00 (reference)	73	1.00 (reference)	52	1.00 (reference)
4915 to < 5026	214	0.92 (0.78-1.10)	53	0.89 (0.62-1.26)	37	0.83 (0.55-1.27)
5026 to < 5100	58	0.91 (0.69-1.20)	19	1.14 (0.69-1.89)	16	1.29 (0.74-2.26)
≥ 5100	44	0.58 (0.42-0.80)	7	0.36 (0.17-0.78)	12	0.86 (0.46-1.62)
P_{trend}		.01‡		.07		.74
Median UVR						
< 4915	188	1.00 (reference)	52	1.00 (reference)	33	1.00 (reference)
4915 to < 5026	165	1.06 (0.86-1.30)	33	0.76 (0.49-1.17)	28	0.99 (0.60-1.64)
5026 to < 5100	137	0.87 (0.70-1.08)	42	0.97 (0.65-1.45)	25	0.85 (0.51-1.42)
≥ 5100	110	0.79 (0.63-1.00)	25	0.64 (0.40-1.03)	31	1.20 (0.74-1.96)
P_{trend}		.05‡		.12		.66
Maximum UVR						
< 4915	163	1.00 (reference)	44	1.00 (reference)	26	1.00 (reference)
4915 to < 5026	94	1.11 (0.86-1.42)	22	0.95 (0.57-1.58)	22	1.53 (0.87-2.68)
5026 to < 5100	130	1.03 (0.82-1.29)	31	0.90 (0.57-1.43)	21	1.00 (0.56-1.77)
≥ 5100	213	0.88 (0.72-1.07)	55	0.83 (0.56-1.24)	48	1.14 (0.71-1.83)
P_{trend}		.18		.36		.75

*Case counts are classified according to the exposure category at the time of diagnosis.
†All models were adjusted for age (as timescale) and calendar-year effects.
‡$P_{nonlinearity} > .05$.

Table 5. RRs with 95% CIs for associations of time-dependent average annual residential UVR in a 20-km radius, categorized into California statewide quartiles, with risk of CLL/SLL, MM, and HL

Average annual residential UVR in a 20-km radius (W-h/m²)	Chronic lymphocytic leukemia/small lymphocytic lymphoma		Multiple myeloma		$P_{heterogeneity}$ by lymphoma subtype‡	Hodgkin lymphoma	
	Cases (n)*	RR (95% CI)†	Cases (n)*	RR (95% CI)†		Cases (n)*	RR (95% CI)†
Minimum UVR							
< 4915	58	1.00 (reference)	57	1.00 (reference)		27	1.00 (reference)
4915 to < 5026	48	1.03 (0.71-1.50)	36	0.76 (0.51-1.16)			
5026 to 5100	7	0.54 (0.25-1.18)	11	0.82 (0.43-1.57)		10	1.26 (0.61-2.61)
≥ 5100	7	0.46 (0.21-1.01)	10	0.71 (0.37-1.35)	.29		
P_{trend}		.08		.15			
Median UVR							
< 4915	39	1.00 (reference)	43	1.00 (reference)		14	1.00 (reference)
4915 to < 5026	35	1.15 (0.73-1.80)	29	0.81 (0.51-1.29)			
5026 to < 5100	28	0.88 (0.55-1.43)	17	0.45 (0.26-0.79)		23	1.67 (0.86-3.26)
≥ 5100	18	0.64 (0.37-1.12)	25	0.79 (0.48-1.28)	.11		
P_{trend}		.17		.08			
Maximum UVR							
< 4915	35	1.00 (reference)	39	1.00 (reference)		10	1.00 (reference)
4915 to 5026	19	1.11 (0.64-1.92)	20	1.07 (0.63-1.80)			
5026 to < 5100	26	1.00 (0.60-1.65)	22	0.72 (0.43-1.21)		27	1.63 (0.79-3.37)
≥ 5100	40	0.79 (0.50-1.24)	33	0.57 (0.36-0.90)	.73		
P_{trend}		.30		.01§			

*Case counts are classified according to the exposure category at the time of diagnosis.
†All models were adjusted for age (as timescale) and calendar-year effects.
‡Lymphoma subtypes include diffuse large B-cell lymphoma, follicular lymphoma CLL/SLL, and MM.
§$P_{nonlinearity} > .05$.

Discussion

In this large, prospective cohort study of California women, we found that living in an area with higher ambient UVR was associated with a significantly reduced risk of NHL, especially DLBCL and CLL/SLL, as well as MM, but not FL or HL. The generally stronger associations with minimum rather than median or maximum residential UVR may suggest that being exposed to a consistently high customary, basal level of ambient UVR, rather than intermittent bouts of intense exposure, is protective against these lymphoid malignancies. The inverse association was not modified by skin sensitivity to sunlight, race/ethnicity, body mass index, or neighborhood SES. Skin sensitivity also was not an independent predictor of risk of lymphoid malignancies, but blistering sunburns may have increased the risk of FL in particular. Unlike some prior studies,[23,24] we did not detect an increased risk of NHL or HL among women with a history of melanoma or other skin cancer. Vitamin D from diet, a relatively minor contributor to circulating 25-hydroxyvitamin D levels compared with UVR-related characteristics,[25] was also unassociated with risk of lymphoid malignancies. Taken together, our results suggest that higher routine residential UVR exposure may protect against the development of DLBCL, CLL/SLL, and MM in women through a mechanism independent of vitamin D production or by increasing bioactive vitamin D levels beyond those typically achieved through the intake of food and supplements by women in this cohort.

Our findings about residential UVR are largely consistent with findings from most case-control studies of NHL, including a pooled analysis of 10 studies with a combined total of 8243 cases and 9697 controls from the United States, Europe, and Australia,[2] as well as additional studies in upstate New York[26] and Greece (focusing on childhood NHL),[27] all of which found inverse associations between recreational sun exposure and NHL risk. However, the InterLymph pooled analysis found no association with occupational sun exposure,[2] and a later French case-control study[28] and 2 prospective cohort studies found no association between residential, workplace,[5] or personal recreational UVR exposure[6] and NHL risk, contradicting our findings and those of others. The discrepancy in results from those of the other 2 cohort studies may be due in part to a more accurate measure of ambient UVR in our study than in that by Adami et al,[5] who used only geographic latitude to classify potential UVR exposure. In California, for example, altitude (which is independent of latitude) is a stronger predictor than latitude of ground-level UVR.[12] Other explanations for the different results may include higher levels and greater heterogeneity of ambient UVR exposure across California (where broad differences in latitude, altitude, and reflectance contribute to a wide range of UVR levels) than across Sweden (where average daily total global solar radiation is ~ 3000 W-h/m² for most of the country)[29] or differences in actual UVR exposure received between day-to-day activities in the proximity of one's home (as measured in our study) and overall recreational activities, including intermittent, intense exposure as part of vacation travel to sunny areas and routine use of artificial tanning devices (as measured by Veierød et al[6]). However, Veierød et al[6] also observed lower NHL risk among women with a higher propensity to sunburn, whereas we did not, suggesting differences because of exposure measurement error or confounding. Our results also contrast with a handful of mixed positive and null results for MM[28,30] and mixed inverse and null results for HL.[23,27,28,30]

Most case-control studies that found an apparent protective effect of UVR against NHL development have pointed to the potential antilymphomagenic effects of UVR-mediated vitamin D production, a biologic pathway that is supported by several lines of direct and indirect evidence. First, bioactive vitamin D promotes differentiation and inhibits proliferation of lymphoma cells in vitro[31] and plays a key role in maintaining homeostasis of normal B cells.[3] Most lymphocytes express the vitamin D receptor,[32] providing a direct mechanistic link between vitamin

Table 6. RRs with 95% CIs for associations of time-dependent minimum annual residential UVR in a 20-km radius, categorized into California statewide quartiles, with risk of overall NHL, stratified by sun sensitivity, sun exposure, and other characteristics

Minimum average annual residential UVR in a 20-km radius (W-h/m^2)	Cases (n)*	RR (95% CI)†	Cases (n)*	RR (95% CI)†	$P_{interaction}$
	Severe burn after 1 h in hot sun		**Mild or no burn after 1 h in hot sun**		
< 4915	84	1.00 (reference)	193	1.00 (reference)	
4915 to < 5026	83	1.13 (0.84-1.53)	130	0.83 (0.66-1.03)	
5026 to < 5100	21	1.06 (0.66-1.70)	34	0.80 (0.56-1.15)	
≥ 5100	19	0.97 (0.60-1.57)	25	0.50 (0.33-0.75)	.16
P_{trend}		.73		< .01‡	
	Light or no tan after repeated sun		**Moderate or deep tan after repeated sun**		
< 4915	84	1.00 (reference)	189	1.00 (reference)	
4915 to < 5026	67	0.96 (0.70-1.32)	141	0.90 (0.72-1.12)	
5026 to < 5100	11	0.55 (0.30-1.04)	44	1.00 (0.72-1.39)	
≥ 5100	18	0.84 (0.51-1.38)	26	0.53 (0.35-0.79)	
P_{trend}		.25		.02‡	.17
	Ever severely sunburned with blistering		**Never severely sunburned with blistering**		
< 4915	195	1.00 (reference)	83	1.00 (reference)	
4915 to < 5026	145	0.90 (0.73-1.11)	69	1.04 (0.76-1.43)	
5026 to < 5100	32	0.72 (0.50-1.04)	23	1.32 (0.83-2.10)	
≥ 5100	33	0.61 (0.42-0.89)	11	0.54 (0.29-1.01)	.21
P_{trend}		.01‡		.47	
	History of melanoma or other skin cancer		**No melanoma or other skin cancer**		
< 4915	38	1.00 (reference)	246	1.00 (reference)	
4915 to < 5026	32	0.94 (0.59-1.50)	182	0.89 (0.73-1.07)	
5026 to < 5100	13	1.43 (0.77-2.64)	45	0.79 (0.58-1.09)	
≥ 5100	12	1.21 (0.64-2.26)	32	0.50 (0.35-0.72)	.09
P_{trend}		.52		< .01‡	
	Non-Hispanic white		**Other race/ethnicity**		
< 4915	259	1.00 (reference)	23	1.00 (reference)	
4915 to < 5026	185	0.90 (0.75-1.08)	27	1.19 (0.69-2.06)	
5026 to < 5100	55	0.93 (0.70-1.24)	3	0.75 (0.22-2.50)	
≥ 5100	41	0.59 (0.43-0.82)	3	0.57 (0.17-1.90)	
P_{trend}		.01‡		.65	.69
	Body mass index ≥ 25 kg/m^2		**Body mass index < 25 kg/m^2**		
< 4915	116	1.00 (reference)	145	1.00 (reference)	
4915 to < 5026	89	0.89 (0.68-1.17)	115	0.97 (0.76-1.24)	
5026 to < 5100	23	0.82 (0.53-1.29)	32	1.02 (0.70-1.48)	
≥ 5100	19	0.58 (0.36-0.93)	23	0.65 (0.42-1.00)	.86
P_{trend}		.03‡		.20	
	Deciles 8-10 of statewide SES		**Deciles 1-7 of statewide SES**		
< 4915	184	1.00 (reference)	96	1.00 (reference)	
4915 to < 5026	132	0.90 (0.72-1.13)	81	0.97 (0.73-1.30)	
5026 to < 5100	22	0.80 (0.52-1.24)	36	1.09 (0.75-1.60)	
≥ 5100	11	0.43 (0.23-0.79)	33	0.75 (0.51-1.12)	.38
P_{trend}		.02‡		.35	

*Case counts are classified according to the exposure category at the time of diagnosis.
†All models were adjusted for age (as timescale) and calendar-year effects.
‡$P_{nonlinearity} > .05$.

D and immune cell behavior. Second, the autoimmune conditions rheumatoid arthritis and multiple sclerosis, which are believed to promote lymphomagenesis through chronic inflammation and antigenic B-cell stimulation,[33] are convincingly inversely associated with UVR exposure, serum dihydroxyvitamin D levels, and vitamin D intake,[34,35] and may share common causative pathways with lymphoid malignancies.[36] Finally, some genetic variants of the vitamin D receptor, which can have functional effects on immune cell behavior in vitro,[37] are associated with risk of certain NHL subtypes, and may modify risk associations with UVR.[38-40]

However, a pooled analysis of 10 prospective cohort studies recently found no association between prediagnostic serum 25-hydroxyvitamin D and risk of NHL or its major histologic subtypes,[41] providing a solid argument against the vitamin D hypothesis. Instead, given the null associations that we detected with vitamin D, calcium, retinol, seafood, and dairy products (or, in the case of MM risk, an inverse association with dairy intake), as well as the lack of modification of the UVR association by characteristics that affect circulating vitamin D levels, the observed apparent protective effect of residential UVR may be mediated by other pathways independent of vitamin D. Such pathways may involve subclinical immunosuppression, perhaps through UVR-mediated induction of regulatory T cells,[42] which are critical to maintaining normal immune homeostasis and to inhibiting inflammation.[43] Alternatively, the single measure of serum 25-hydroxyvitamin D in the pooled cohort analysis and the estimates of total and dietary vitamin D intakes in our study may not have been sufficient to

capture vitamin D status, or vitamin D levels in these study populations may not have been adequate to achieve a protective effect.

Our results should be interpreted in light of other potential explanations, including some study limitations. We lacked information on individual-level UVR exposure history, including indoor and outdoor suntanning habits and participation in outdoor recreational activities, and were therefore unable to differentiate between chronic and intermittent or mild and intense exposure to UVR, which may have distinctive causative effects. As a result, we could not examine such UVR-related behaviors as main effects or potential confounders. Given that UVR exposure misclassification was most probably nondifferential for the outcomes of interest, results were probably biased toward the null. In addition, most cohort members resided in geographic areas toward the upper range of statewide UVR exposure, reflecting residential patterns in California; therefore, we lacked sufficient heterogeneity to compare extremes of residential UVR exposure, which may be more strongly associated with risk of lymphoid malignancies than we observed. We also did not collect information on individual-level SES and, therefore, could adjust only for neighborhood-level SES, which, although useful for detecting socioeconomic gradients in health,[44] may have permitted residual confounding by other SES factors. SES, in turn, is known to influence sun-related behaviors and cultural norms, such as vacation travel to sunny areas, routine outdoor recreational activities, and preferences for tanned skin.[45] Although we had detailed information on skin sensitivity to sunlight, the potential influence of skin type on UVR exposure is unclear, because lighter skin permits a higher level of vitamin D synthesis in response to a given amount of UVR exposure,[46] yet persons prone to sunburns might also take more precautions to avoid the sun. Indeed, our measure of sunburn blistering did not distinguish participants who were exposed but did not blister from participants who avoided sufficient exposure to cause blistering.

We also lacked information on residential history before cohort entry and consequently could not estimate associations with age-specific or cumulative lifetime UVR exposure. Nevertheless, our estimate of residential UVR at baseline probably captured a large portion of adulthood exposure, given that an analysis of residential mobility in the CTS showed that the average duration at one's baseline address was 15.1 years,[47] and 61% of the analytic cohort remained at their baseline address at the end of follow-up. Furthermore, we also found no difference in results that were based on participants' current, updated residential address during $\geq$ 12 years of follow-up compared with their baseline address only, reflecting the residential stability of the cohort. However, we were unable to estimate UVR levels at other locations, such as workplaces and common recreational destinations, frequented by cohort members, and we did not account for ambient UVR exposure $>$ 20 km from one's residence.

A further limitation is the modest number of cases, particularly of specific NHL subtypes, MM, and HL, which may have prevented us from detecting moderate associations or interactions with any of the exposures examined. Conversely, as in any observational study, the associations that we did observe may have been because of chance or residual or unmeasured confounding.

These limitations are countered by the substantial strengths of our study, including the prospective study design, detailed covariate data for evaluation of confounding and effect modification, complete and accurate follow-up for incident lymphoid malignancies, and a validated measure of residential UVR at baseline and subsequent addresses, including a 20-km buffer to allow for local mobility. In addition, the range of residential UVR exposure in our California-based cohort was wide: average ambient UVR levels across the continental United States vary from a low of 2858 W-h/m^2 to a high of 5816 W-h/m^2,[12] whereas neighborhood UVR levels in the CTS cohort ranged between 3838 and 5785 W-h/m^2. Thus, the cohort covered most of the nationwide variability in residential UVR (except for the lowest levels), enabling us to assess extremes of UVR exposure that are relevant to the overall United States.

In summary, with the use of high-quality, prospective data, we found that higher routine exposure to UVR, as estimated by ambient UVR in the vicinity of one's residence, may reduce the risk of overall NHL, DLBCL, CLL/SLL, and MM in women, whereas FL and HL may have a different causative relation with UVR. The lack of an association with skin type or dietary vitamin D intake may point to confounding, measurement error, or a vitamin-D–independent pathway between UVR and lymphomagenesis. Given that exposure to UVR is an established risk factor for melanoma and nonmelanoma skin cancer,[48] augmenting UVR exposure is unlikely to be accepted as a viable means of reducing lymphoma risk on a population level. Instead, better understanding of the pathways by which UVR may decrease the risk of lymphoid malignancies could point to other interventions, such as use of probiotics to induce regulatory T-cell activity,[49] to reduce the occurrence of these cancers.

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Authorship

Contribution: E.T.C. designed the research and drafted the manuscript; A.J.C. performed the statistical analysis; M.C., L.B., and P.L.H.-R. collected data; E.T.C., A.J.C., M.C., Y.L., S.S.W., L.B., C.A.C., and P.L.H.-R. interpreted the results; E.C., L.B., and P.L.H.-R. obtained funding for the research; and A.J.C., M.C., Y.L., S.S.W., L.B., C.A.C., and P.L.H.-R. critically reviewed and revised the manuscript.

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